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THE INFLUENCE OF VITAMIN D ON COVID-19 OUTCOMES

Chapter 4 of Covid-19 and Nutraceuticals: A Guidebook

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"Light is sweet and it pleases the eyes to see the sun."
— Solomon
Hebrew King and Philosopher

ABSTRACT

Most of the world's population has vitamin D levels which are suboptimal for healthy immune system function. Recent recommended goals are far higher than legacy guidelines, which are based entirely upon promoting bone health, rather than on supporting all the many other functions of vitamin D. Vitamin D strengthens the innate immune response, decreasing the likelihood of infection from SARS-CoV-2 exposure. Vitamin D also regulates the adaptive immune system and inflammation. Thus, with appropriate levels, infected persons have a reduced likelihood of developing hyperinflammatory (severe) Covid-19 (the cytokine or bradykinin "storm"). Many experts have noted that vitamin D plays a role in preventing every one of the disorders associated with severe Covid-19. In addition, the risk factors for getting severe Covid-19 are identical to the risk factors for becoming vitamin D deficient. Evidence of a link between low vitamin D levels and poor Covid-19 outcomes is robust, including numerous population and individual correlational studies, causal modeling, prospective cohort intervention studies, and randomized controlled trials.

I. Background

The industrial revolution led physicians such as Sniadecki (in Poland, 1840) to notice that sunlight is protective for human health.[1] He noticed that children living in the crowded, polluted city of Warsaw developed rickets, while children living in the nearby countryside remained rickets-free.[1] The hypothesis that sunlight on skin could influence the deep tissues and bones was initially met with skepticism, but the evidence became undeniable: in 1900 over 90% of European urban children and 80% in Boston suffered from rickets.[1] Though cod-liver oil had been used to treat and prevent rickets for years, in the early 1900s, UV-irradiated fat ("vitamin D") was identified as another cure.[1,2] In 1928, Adolf Windaus was awarded the Nobel Prize for discovering "vitamin D."[2,3] In 1936 it was discovered that UV light from sunshine produced D_3 in the skin, which is then converted by the body to biologically active 25(OH)D, which means that "vitamin" D is, in fact, a steroid.[2]

In 1979, a team led by Stumpf discovered Vitamin D receptors throughout the body, revealing that vitamin D is important for more than just skeletal calcium maintenance.[1] Evidence gradually emerged that vitamin D is among the most powerful of the micronutrients, with receptors in virtually every body system.[4] Through its local actions (autocrine and paracrine signaling), vitamin D helps regulate processes as varied as insulin production, apoptosis, and innate and adaptive immunity, thus affecting infectious disease vulnerability and most inflammation-related conditions, including hypertension, diabetes, cancer, arthritis, cardiovascular disease, and autoimmune diseases.[1,5–7]

Prior to the industrial revolution, virtually all of humankind hunted, gathered, farmed, and fished while the days were long, gaining body-weight and storing vitamin D in their fat and muscle tissue.[8] When the dark winter came, opportunities to obtain food diminished. As people lost weight, vitamin D was released, promoting continued good health.[9] The industrial revolution led to a more indoor, often sedentary lifestyle, and more wealth for the masses, so that people with chronically low vitamin D levels gain weight not only during the harvest, but also throughout the winter, without exerting their muscles as much. Their blood "vitamin D" levels drop precipitously, reaching critically low levels by the time the next summer arrives. For example, vitamin D insufficiency is >85% in the winter and spring among pregnant women in Southern England, dropping to 30% in the summer.[10] In Ireland, 24% of the population is vitamin D insufficient (calcifediol <20ng/ml) in summer, more than doubling to 49% in winter [11]. Rare optimal calcifediol levels (>40ng/ml) were found primarily in older women (1-7%), who would be most likely to take supplements year-round for bone health.[11–13]

Because the UVB rays required to produce vitamin D in skin are obstructed by air pollution, clouds, window glass and even ozone when the sun is low (below a 45 degree angle, as is the case in winter, in areas far from the equator, and in the early mornings and late afternoons), and the only significant dietary sources of vitamin D are wild-caught fatty fish (which feed on sunbaked plankton), vitamin D deficiency has traditionally been addressed with food supplementation.[1,14,15] However, supplementation (except in Nordic countries) has decreased over the years, consumption of foods traditionally fortified in some countries, such as cow's milk, is declining, and humans worldwide are adopting an affluent (obese), indoor lifestyle.[16] Individuals with naturally melanin-rich skin who live outside the tropics are rarely able to obtain sufficient vitamin D from the sun.[17] As a person ages, the ability of their skin to produce cholecalciferol decreases.[18] All of these factors led to an alarming vitamin D deficiency pandemic long before Covid-19 appeared on the scene.[16,19,20]

Covid-19 is caused by a novel coronavirus, but the symptoms of severe Covid-19 are not at all without precedent. Respiratory viral illnesses of the past: the Spanish flu of 1918, SARS, and MERS, are quite similar, and even dengue fever has the same basic history of illness.[16,21,22] In each case, the initial viral illness is mild or asymptomatic for most people, with some sufferers developing symptoms more like influenza. However, as they appear to be recovering (and their viral load is dropping), a few people suddenly take a turn for the worse, because their immune system over-reacts.[23,24] This immune system overreaction, not the virus itself, causes life-threatening hyper-inflammation.[22,23] In the case of Covid-19, macrophages, cytokines, and fibroblasts fill the lungs, which leads to difficulty breathing.[23,25–27] The increased inflammation can also lead to blood clots and organ damage.[23,26] We know the virus itself is not the proximate cause of this organ damage because researchers do not find viable virus in the blood of Covid-19 sufferers, even when they have severe Covid-19.[26,28,29] The rare exceptions seem to be when the virus is forced into the blood stream from the lungs by high pressure ventilator treatment.

It is well known that vitamin D helps prevent chaotic immune responses such as those characteristic of severe Covid-19 (the cytokine or bradykinin "storm").[30] Therefore, it should be expected that many Covid-19 sufferers will have low levels of vitamin D. Already by March, 2020, dozens of published studies demonstrated that low vitamin D levels lead to poor Covid-19 outcomes.[16] As of June 2021, a link between low vitamin D levels and poor Covid-19 outcomes was asserted in ~3000 published studies and biological plausibility discussions in MEDLINE indexed journal articles, including hundreds of population and case correlational studies, causal modeling, RCTs, and prospective cohort intervention studies. At this point, multiple meta-analysis author groups have concluded that there is a significant relationship between 25(OH)D serum levels and Covid-19 infection, severity and/or mortality.[4,31,32]

II. **Classification of vitamin D levels and why low levels are common**

A. Defining Vitamin D

Confusion about vitamin D complicates the design and obscures the interpretation of research studies.[33] Four different molecules are commonly called vitamin D. (See Figure 1, page 4)

a) **Cholecalciferol**, or vitamin D_3, is produced when UVB light (primarily 295-300nm) acts on 7-dehydrocholesterol in the skin to break the ring between carbon 9 and 10. Wild caught salmon and other fatty fish whose food-chain begins with sun-exposed plankton are rich in D_3; far lesser amounts are found in free-range eggs and cheese.[30] However, without added UVB skin synthesis or supplements, only an almost exclusively wild fish diet will provide adequate vitamin D. Cholecalciferol is the most common vitamin D supplement, easily extracted from sheep lanolin. Before this process was discovered, **Ergocalciferol,** or vitamin D_2, supplements were common. Ergocalciferol, which is one third as potent as cholecalciferol, is formed in modest amounts when mushrooms or yeast are irradiated with UVB light.[34] Fruits and vegetables do not contain significant vitamin D. In some countries, foods are fortified with vitamin D_2 or D_3, but often at only modest levels. Because cholecalciferol, which stabilizes the endothelium and is in itself anti-inflammatory, and has a half-life of only 24-50 hours, sunshine and/or D_3 supplement intake should ideally be daily, rather than at less frequent intervals.[3,6,35]

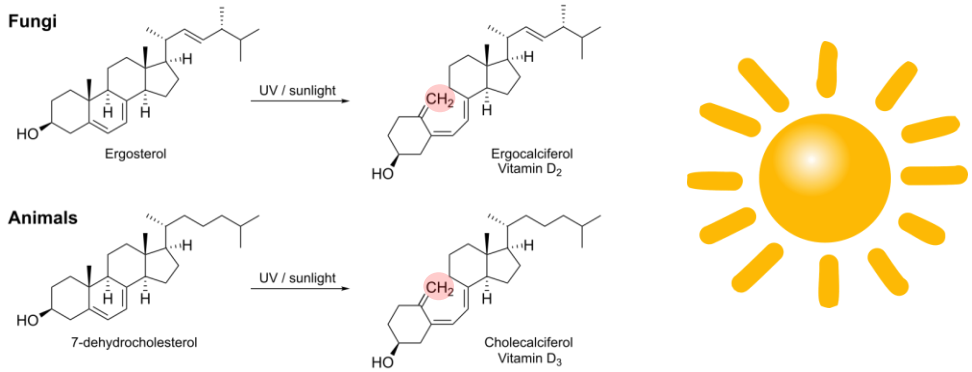
b) Calcifediol, 25(OH)D, 25hydroxyvitaminD, and calcidiol are all names for the form of vitamin D that is produced when the enzymes CYP2R1, CYP27A1, etc. in the liver replace the H with an OH group at the 25 position of cholecalciferol.[36,37] Ergocalciferol is converted to calcifediol as well, but the process is less efficient. Because **c**alcifediol has a half-life of about two weeks, appropriately increased weekly vitamin D intake provides almost as many benefits as daily.[38]

c) Calcitriol, also called 1,25OHD or $1,25(OH)_2D$, is produced when CYP27B1 replaces the H at the 1 position in calcifediol with another OH. This tightly regulated process takes place in the kidneys for circulating calcitriol used in calcium transport, but it also takes place in other organs, monocytes, and macrophages (see diagram).[39] The vitamin D receptors found throughout the body are activated only by calcitriol and its analogs.[37]

The ubiquitous enzyme CYP24A1, induced by high calcitriol levels, adds an OH to the 24 position of calcifediol and calcitriol. This irreversible process leads to the formation of **calcitroic**

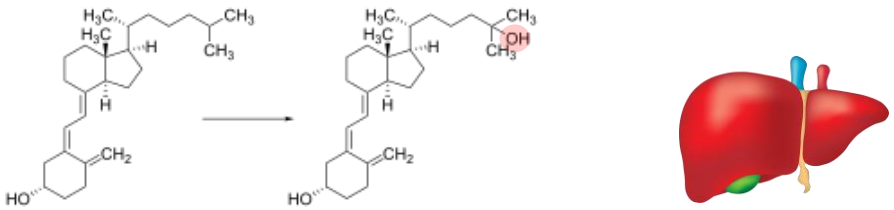
acid, which aids in callus formation for fracture healing, but appears to be otherwise inactive and is rapidly excreted, protecting against toxic vitamin D levels.[37,40] A single bolus dose of cholecalciferol can lead to increased calcitroic acid production for at least 28 days.[41]

Figure 1: Forms of vitamin D

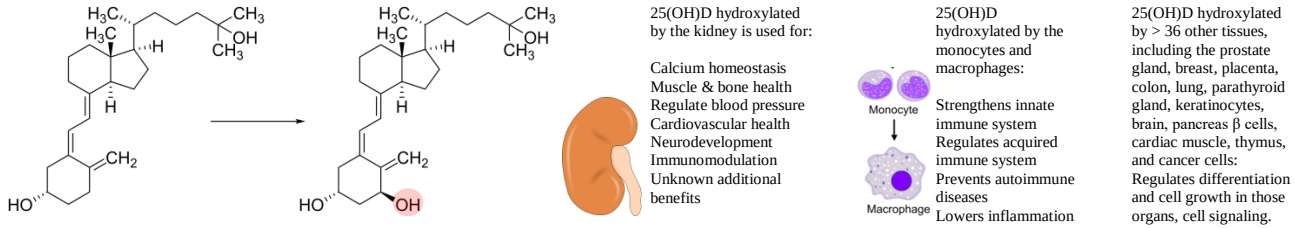


The photochemistry of vitamin D biosynthesis in animal and fungi: UVB light breaks the ring between C 9 & 10

Note: In general, plants do not contain the cholesterol needed to synthesize vitamin D. Vitamin D_2 (fungi) is one-third the potency of vitamin D_3.



Liver hydroxylation of cholecalciferol (D_3) to calcifediol, which is 25(OH)D: H at position 25 is replaced with OH



Kidney hydroxylation of calcifediol to calcitriol, which is 1,25(OH)$_2$D: H at position 1 is replaced by OH
(Calcitriol is also formed, in lesser quantities, in the monocytes & macrophages, and in the many tissues with vitamin D receptors)

Circulating CYP24A1 adds an OH to the 24 position of calcifediol and calcitriol in response to high calcitriol levels to form calcitroic acid, which is excreted, helping protect against toxicity. Calcitroic acid can be mistaken for calcifediol by many tests for 25(OH)D.

Molecular diagrams By: Hbf878 – Own work CC0, modified by Robin Whittle, used with permission, all other images CC with no attribution required

Differences in units used to report blood levels of vitamin D and to discuss supplement dosages can also be confusing. Serum 25(OH)D is reported in either ng/ml or nmol/L. To convert ng/ml to nmol/L, multiply by 2.5 (20ng/ml = 50nmol/L). For vitamin D_3 taken by mouth, the conversion factor from mcg to IU is 40 (50mcg = 2000IU).

Although cholecalciferol and calcifediol both circulate in the blood, cholecalciferol is more easily absorbed into muscle and fatty tissue.[8,36] Serum vitamin D tests measure total calcifediol, but most are cross-reactive with calcitroic acid that has not yet been excreted, which can mislead researchers.[36] Calcifediol, rather than cholecalciferol, supplements are appropriate

for individuals with chronic kidney disease, because their elevated parathyroid levels inhibit the conversion process in the liver.[42] Individuals with liver failure may also require calcifediol.[36]

Recently it has been learned that giving calcifediol rather than cholecalciferol also leads to a much faster and a 3-6 times larger increase in available active vitamin D (calcitriol).[42,43] This has significant implications for remedying vitamin D deficiency in acutely ill patients, as it can take up to 7 days for large doses of cholecalciferol to be converted to calcifediol naturally, and a much higher percentage is lost to storage in the fatty tissue.[42] However, raising calcifediol levels too rapidly can cause rapid catabolism while dramatically increasing calcium levels.[37] As was mentioned earlier, this catabolism may mislead researchers who are unaware of the fact that most 25(OH)D tests do not distinguish between circulating calcifediol and unexcreted calcitroic acid [36]. Therefore, extended release calcifediol or multiple moderately high doses should be used.[37] Research into the reasons intensive care patients often require 10 – 100 times the normal dose of cholecalciferol to raise their 25(OH)D levels above 20ng/ml is ongoing, but it appears related to decreased CYP2R1 activity induced by fasting, diabetes, obesity, exposure to high-dose glucocorticoids, illness, and other factors.[39]

B. Recommended serum levels and intake goals from organizations and governments

Most legacy public health guidelines for target serum vitamin D levels, based entirely upon supporting bone health, define <10-12ng/ml 25(OH)D as "vitamin D deficient" and <20ng/ml as "vitamin D insufficient."[16] However, clinical practice guidelines that take into account the many other functions of vitamin D widely recognize that levels below 30ng/ml are insufficient.[10,37,44] Most researchers define 25(OH)D levels below 20ng/ml as deficient.[16,44] Parathyroid levels are elevated for all races, which would logically indicate that a deficiency exists, when 25(OH)D is below 32ng/ml.[45–47] When living a traditional lifestyle in the tropics, the Hadzabe and Maasai of East Africa have mean 25(OH)D levels of close to 50ng/ml, as do lifeguards [48,49]. Both surgical and hospital-acquired infection rates plateau at very low levels when 25(OH)D levels reach 50ng/ml.[12] Researchers evaluating 191,779 PCR test results from a laboratory database found that Covid-19 positivity rates also plateau at very low levels when 25(OH)D reach 50ng/ml.[50] (See Figures 2 and 3, page 6)

The National Academy of Medicine, the UK's NICE and most other public health policy organizations recommend age-dependent daily intakes of vitamin D_3 in the range of 100 – 800IU, with a goal of reaching serum 25(OH)D levels of 20 – 50ng/ml.[51,52] However, two groups of researchers have evaluated the data and concluded that the statistical calculations used to determine these recommended intakes contain an error.[51,53] A third group agreed, finding that the recommended vitamin D_3 intake for adults to reach only the minimal 20ng/ml serum levels needed for bone health could be over 7000IU/day.[54,55] Because circulating levels of 30ng/ml or greater are required for the immune cells to convert calcifediol to calcitriol, 40-60ng/ml is recommended.[7,56]

The Endocrine Society recommends 2000IU of vitamin D_3 daily for most adult patients to reach their minimum target 25(OH)D level of 30ng/ml, but acknowledges 4000 – 6000IU/day may be required for obese and malabsorptive patients, and that up to 10,000IU/day is safe.[7,51] Recent research exploring the role of vitamin D in maintaining immune health, regulating inflammation, and helping prevent autoimmune diseases, cancers, allergic disorders, infections, skin diseases, neuropsychiatric disorders, and cardiovascular disease has led to further support for higher supplementation recommendations.[57] Serum 25(OH)D levels of 40-60ng/ml are now considered optimal for immune health, and even higher levels are recommended for treating

autoimmune and many other serious health conditions.[7,45,46,58,59] Vitamin D's critical autocrine signaling requires 25(OH)D concentrations of 40-60ng/ml to function properly.[7]

Figure 2: Relationship between circulating 25(OH)D level and COVID-19 positivity rate[50]
(from Kaufman, et al., PLOS ONE, 2020, an open source publication)

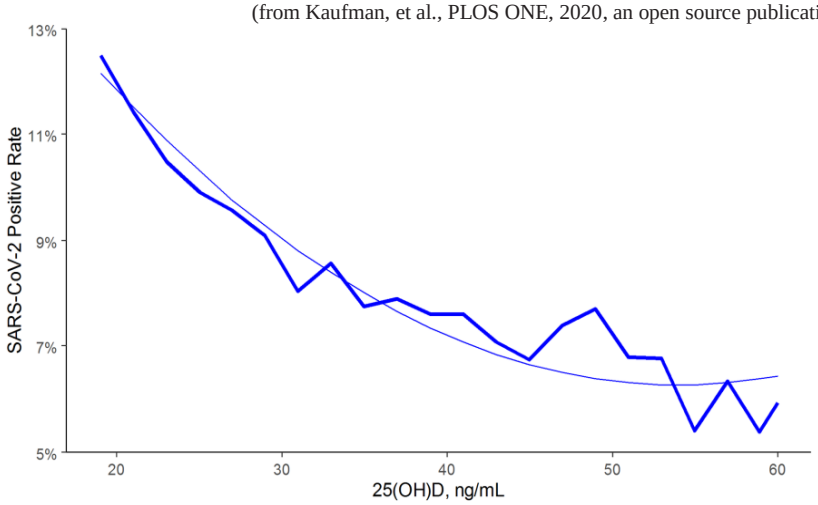
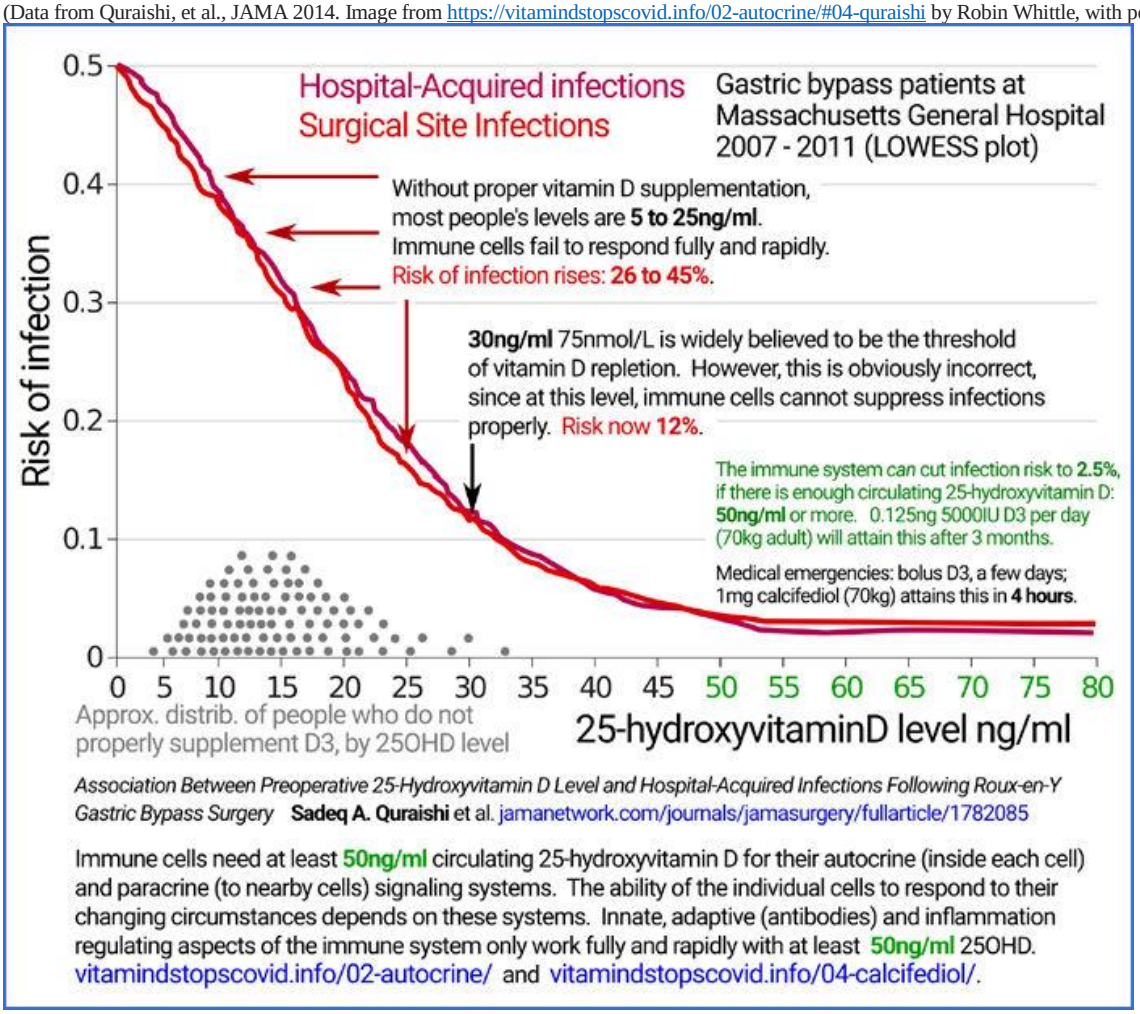


Figure 3: Relationship between circulating 25-hydroxyvitamin D levels and risk of infection[12]
(Data from Quraishi, et al., JAMA 2014. Image from https://vitamindstopscovid.info/02-autocrine/#04-quraishi by Robin Whittle, with permission)



The vitamin D deficiency pandemic began long before Covid-19 appeared on the scene.[16,52,60] In the USA, in Minnesota (44°N), 60% of the immigrant and refugee population suffer from vitamin D insufficiency, as do 40% of all Canadians and 56% in the UK.[61] Not surprisingly, the highest risk groups for vitamin D deficiency mirror the those of severe Covid-19: people who are elderly (particularly those living in care homes), obese, hypertensive, diabetic, male, have naturally melanin-rich skin and live outside the tropics, or those who live in areas with high levels of air pollution.[16,17,22,62]

Despite this, many public health officials continue to discount vitamin D supplementation during Covid-19, with the WHO recommending 200-600IU, depending upon age, for individuals who are not able to take in sunlight due to lockdowns, and the NHS and British Dietetic Association continuing to suggest 400IUs for sun-starved adults.[63–65] As of 5 Sept 2021, the US NIH had no official stance on vitamin D for the prevention or treatment of Covid-19, noting that deficiency is the most common in groups that are hardest hit by Covid-19 and biological plausibility is strong, but there is a theoretical risk for toxicity with high doses; the only study cited is one in which the authors of the page themselves note that vitamin D_3 was given to patients very late in their illness.[62]

A hypothetical concern for toxicity (serum 25(OH)D>150ng/ml), often mentioned while stating that vitamin D is a fat soluble vitamin (harkening to vitamin A) is the main reason given for not recommending population-wide vitamin D supplements.[66] However, vitamin D toxicity is far more rare than vitamin A toxicity, in part because of the built in fail-safe described earlier.[37] What is called vitamin D toxicity is, in fact, calcium toxicity, and it occurs only in extreme situations: when calcium intake is far too high; when the person has serious calcium-altering diseases (e.g., primary hyperparathyroidism, tuberculosis, lymphoma, sarcoidosis, or other granulomatous disorders); or when the person ingests doses of vitamin D in excess of 20 times the upper recommended dose of 10,000IU for prolonged periods of time, which has happened historically primarily as a result of errors in manufacturing, labelling, or prescribing.[66,67]

Even when hypervitaminosis D occurs, treatment is simple and permanent damage is rare.[68,69] A large ecological study of high vitamin D supplementation took place by accident when in 1990-1992 a dairy in the Boston area accidentally fortified milk with 230,000IU/quart instead of 400IU/quart: 575 times the intended amount.[70] The overage remained undiscovered for two years, as despite taking in this high dose day after day most customers did not become ill; but eventually Boston area emergency departments linked the resultant approximately 19 cases of vitamin D toxicity to the dairy.[70,71] The only sufferer who did not recover died of pneumonia due to immune compromise from the prednisone given her as treatment, rather than from effects of hypercalcemia.[70,72] The jury found that the dairy's dramatic error did not cause the decedent's death.[72]

Virtually all experts agree that up to 10,000IU/day of D_3 is safe, long-term.[66,67,73] Studies of vitamin D supplementation consistently find no differences in adverse events between controls and treatment groups, despite up to 50,000IU/day being given, long-term.[46,74–76] Patients receiving short-term high dose (60,000IU/day) vitamin D_3 therapy for Covid-19 raised their 25(OH)D levels to 39-113ng/ml without a significant increase in their calcium levels.[77,78]

III. Biological Plausibility: How vitamin D's known mechanisms of action relate to Covid-19

Multiple vitamin D functions are relevant to Covid-19 outcomes. At the most basic level, vitamin D reinforces natural barriers against respiratory tract invaders, preserving the tight, gap,

and adherin junctions between epithelial cells.[52,79,80] Vitamin D strengthens the innate immune response, significantly decreasing the likelihood of exposed individuals becoming ill with a respiratory virus at all, with modest daily doses being far superior to larger monthly doses.[74,76,81] Vitamin D also controls the adaptive immune response, providing a robust response to the viral threat while calming excess inflammation, which should help prevent the acute respiratory distress syndrome (ARDS) that is responsible for ~70% of Covid-19 fatalities.[77,81–83] Through its regulation of the renin-angiotensin system (RAS), vitamin D directly limits the initial severe Covid-19 complication, ARDS.[22] Vitamin D also protects against thrombolytic events, which affect 28% of ICU patients with Covid-19.[22,82,84] Therefore, one should expect individuals with higher vitamin D levels to be less likely to test positive for Covid-19, to be hospitalized due to Covid-19, to require ICU or ventilator care, and to die of Covid-19. The evidence, reviewed later in this chapter, supports this expectation.[16]

Optimal 25(OH)D levels can more than halve the incidence and significantly reduce the duration of acute respiratory infections by enhancing the innate immune response, including increasing vitamin D dependent antimicrobial peptides, such as cathelicidins and defensins.[81,85,86] Cathelicidin LL-37 is antiviral, and it also helps regulate inflammation during illness.[31,87] Supplementation with 4000IU/day of vitamin D decreased dengue virus infection.[88]

The adaptive immune response to SARS-CoV-2 relies upon memory and regulatory T cells, which are heavily dependent upon adequate vitamin D levels.[81,89] People who have had asymptomatic or mild Covid-19 have robust memory T cell immunity which persists post infection.[90] In contrast, patients who died of severe Covid-19 had impaired T cell responses, which would permit auto-immune responses while allowing the SARS-CoV-2 virus to reproduce unchecked.[25,90] Vitamin D regulates the adaptive immune response, recruiting neutrophils, macrophages, and dendritic cells early in the infection while limiting maturation of dendritic cells to prevent excessive inflammation.[91] Vitamin D suppresses excess T helper type 2 cell responses and induces T regulatory cells to inhibit inflammation, improving adaptive immune system functioning.[57]

Vitamin D increases anti-inflammatory cytokines such as IL10 and decreases pro-inflammatory cytokines such as IL1, IL6 and TNFα.[16,32,91] Vitamin D deficient Covid-19 patients had significantly higher serum IL-6, TNFα, and ferritin levels than did patients with higher 25(OH)D.[92] Prospective trials of high-dose daily vitamin D treatment for Covid-19 have also found significant decreases in inflammatory markers (CRP, IL6, LDH, fibrinogen, and ferritin) when compared with pretreatment levels and controls.[77,78] Vitamin D also inhibits MMP-9, bradykinin, and CRP.[83,93] Therefore, one would expect vitamin D to help prevent Covid-19's infamous cytokine or bradykinin "storm".[30,80]

ACE2 receptors, to which SARS-CoV-2 binds in the lungs, are highly expressed on surfactant-producing type 2 pneumocytes.[83] By disrupting these pneumocytes, the virus decreases surfactant production, causing the alveoli to collapse.[83] Calcitriol increases ACE2 expression, which could prevent this complication.[83] ACE2 helps protect the lungs against ARDS.[32] Vitamin D deficiency, which is more common in older males than females in many areas, is associated with increased X-chromosome-linked RAS activity.[22,94] For this reason, males are far more susceptible to ACE2 receptor dysregulation and the resultant hyper-inflammation that is the hallmark of severe Covid-19.[94] This role of vitamin D alone strongly suggests a protective role against severe Covid-19.[22]

Thromboembolism affects 28-50% of Covid-19 patients in the ICU, resulting in significant morbidity and mortality.[22,95] These appear to be cases of anti-phospholipid syndrome,

which is often directly related to low vitamin D.[22] Microcirculatory dysfunction in patients with severe Covid-19 appears to be related to endotheliopathy.[96] Endothelium destabilization by inflammatory cytokines, found in hypertension, diabetes mellitus, chronic renal failure, atherosclerosis, and many other inflammatory diseases, causes dysregulated clotting.[6,91] All of these conditions are associated with low levels of vitamin D, which is known to stabilize the endothelium.[6,16] Vitamin D supplementation has successfully corrected high levels of inflammatory cytokines, including TNF-α, IL-6, and CRP.[83,91] Vitamin D's induction of LL37 would lead to decreased expression of inflammatory IL17, which is abnormally high in Covid-19 and can lead to thrombosis and ARDS.[32] Low vitamin D is also implicated in higher levels of cellular adhesion molecules.[91] Vitamin D supplementation has been shown to decrease thrombus formation directly in high risk patients.[91]

A recent study demonstrated that inadequate vitamin D levels can result in a poor immune response to vaccines in elderly individuals, which has clear implications for recommendations during the Covid-19 pandemic.[97]

IV. Correlational evidence regarding serum vitamin D levels and Covid-19 outcomes

As early as February, 2020, experts were presenting evidence to support the hypothesis that low vitamin D has a dramatic influence on Covid-19 outcomes.[98] It was clear that the populations with the worst Covid-19 outcomes are the exact same populations who tend to have the lowest vitamin D levels: the elderly, males, people with metabolic syndrome-related illnesses like diabetes, obesity, hypertension, and kidney failure, people whose area had just experienced winter, and people with melanin-rich skin who do get not consistent exposure to the tropical sun.[16]

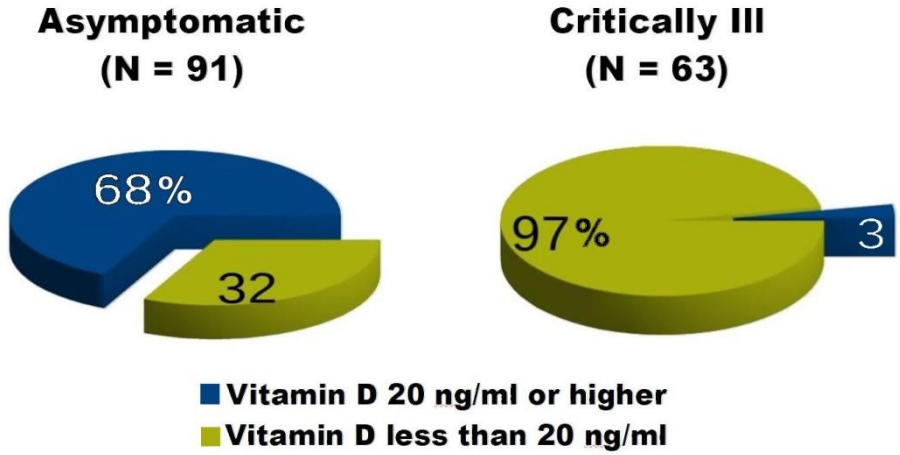
Dramatically, of the first 10 physicians in the UK to die of Covid-19, all had naturally melanin-rich skin, and by the time 119 NHS staff had succumbed, the fact that people with melanin-rich skin living outside the tropics are at much higher risk was undeniable in the USA, as well.[99,100] On 29 April 2020 a communication went out to all "BAME" working doctors in England and Wales, warning them that they could be at high risk for Covid-19 due to vitamin D deficiency, and urging supplementation, including a high loading dose: three days later, the deaths in this group came to an abrupt end.[101] Meanwhile, despite poverty and poor health infrastructure, Africans living in the tropics have still not succumbed in large numbers.[102] Ockham's Razor, "Do not multiply entities without necessity" (The simplest explanation is likely to be true) would appear to apply.[103]

For some vitamin D experts, a devastating viral pandemic had been anticipated; they had long been watching the immune systems of populations around the world become increasingly dysregulated due to lower vitamin D levels, particularly in winter.[60,104,105] Eerily, every symptom of severe Covid-19 could be explained by inadequate vitamin D.[16] Their strong response (there were already 181 scholarly works on the topic by mid-June, 2020) was to document what appeared to be a clear relationship between lower vitamin D levels and worse Covid-19 outcomes in order to persuade public health authorities to support widespread supplementation [16]. This early documentation came primarily in the form of biological plausibility presentations, population (geographical) evidence analyses, prospective correlational studies, and retrospective chart reviews (see links at www.vitaminDforAll.org).[16,106] (Figure 4, page 10)

These forms of evidence have increased daily. Today, in addition to the earlier evidence types, some intervention studies and dozens of meta-analyses and systematic reviews on the

relationship between vitamin D levels and Covid-19 can be found with a quick PubMed search. Only a few examples are detailed here.

Figure 4: Early study demonstrating a dramatic correlation between lower vitamin D levels and worse Covid-19 outcomes.[92] (Figure: original work of Richard Benskin. Data from Jain, et al., *Scientific Reports*. 2020)



A. Evidence based population data (geographical, ecological)

Pugach and Pugach evaluated recent reliable data on the country-wide prevalence of vitamin D deficiency in 10 European countries, finding a statistically significant and linear relationship between prevalence of vitamin D deficiency and deaths/million from Covid-19.[107] Adjusting for the countries' age structure and health expenditures, each 1% increase In severe vitamin D deficiency increased deaths from Covid-19 by 55/million.[107]

Walrand challenged the widely held belief that Covid-19 cases increase in winter due to cooler temperatures.[108] Using automatic fitting software to compare case data for 18 countries against temperature and UV radiation (adjusted for latitude and time of year) 2 weeks prior, he determined that the autumn 2020 "surge" in Covid-19 cases in Europe was completely unrelated to temperatures but was significantly related to decreased sunshine, and predicted that the crisis would continue until spring (which it did).[108,109]

A group of Italian researchers led by Isaia and Diémoz noted that despite uniform exposure prevention measures throughout the country, the Covid-19 pandemic hit northern Italy much harder than it hit southern Italy.[110] A literature search for potential environmental causes yielded UVB for its ability to increase population vitamin D levels.[110] Taking into account air quality, they calculated the UVB exposure for residents in each of the 20 regions from June-Dec 2019: the time leading up to the pandemic.[110] They also compared air temperature, relative humidity, population age, percentage in nursing homes, and potentially relevant comorbidities.[110] Univariate regression found that 74.2% of the variation in Covid-19 fatalities between districts and 41.4% of the variation in cases between districts was explained by vitamin D producing UV light in the preceding months, far more than any other parameter.[110]

A group led by Jayawardena compared population vitamin D deficiency prevalence from the past 10 years (mostly in the past 5 years) with Covid-19 cases and fatalities per million in 24 countries in Asia, an area with dramatically divergent Covid-19 outcomes, as of Dec 31, 2020.[111] Vitamin D deficiency, defined as 25(OH)D<20ng/ml affected over 50% of the adults in three-fourths of these countries, in part due to customs which limit sunlight exposure.[111] Covid-19 cases/million population and fatalities/million were positively correlated with the prevalence of

vitamin D deficiency (cases: r=0.55, p=0.01; fatalities: r=0.50, p=0.01).[111] The variation of total cases and total fatalities can be attributed to vitamin D deficiency at proportions of 33% for cases and 25% for fatalities.[111]

B. **Evidence based on individual data (chart reviews)**

Early chart reviews demonstrating that lower vitamin D levels were correlated with worse Covid-19 outcomes were criticized because it is known that illness can cause vitamin D levels to decline.[4,112] Although this decline would not explain the dramatic differences some of these studies found,[112] more recent studies often use vitamin D levels taken weeks or months prior to infection to eliminate this confounder. The four such studies summarized here all corroborate the conclusions of earlier researchers.

Merzon's group in Israel found that over half (7807) of the 14,022 patients in their health maintenance organization's database who were tested for Covid-19 in Feb-April of 2020 had a previous 25(OH)D level on file.[113] The proportion who tested positive was the same for those with and those without recorded vitamin D levels.[113] After controlling for demographic, psychiatric, and somatic variables, multivariate analysis demonstrated a significant and independent association between 25(OH)D below 30ng/ml and positive PCR results [1.45 (95% CI: 1.08–1.95, $p<0.001$)].[113] Plasma 25(OH)D under 20mg/ml almost doubled the risk of hospitalization due to Covid-19.[113]

Researchers accessed a de-identified laboratory database with 191,779 patients from all 50 US states who had both PCR tests for Covid-19 and 25(OH)D levels from the preceding 12 months, using zip code data to determine race/ethnicity proportions and latitude.[50] Patients with seasonally adjusted 25(OH)D levels below 20ng/ml were significantly more likely to test positive for Covid-19[50] and those with levels ≥55ng/ml were the least likely to test positive.[50] A multivariate logistic model demonstrated that the relationship is robust, remaining significant (OR_{adj} 0.984 per ng/mL increment, 95% C.I. 0.983–0.986; $p<0.001$) when adjusted across latitudes, race/ethnicity, sex, and age ranges.[50]

A large Chicago-based medical center database was mined for a relationship between vitamin D levels within the previous year and positive Covid-19 test results as of Dec 30, 2020.[114] Treatment for deficiency was factored into the results to provide an estimate of concurrent vitamin D levels.[114] A total of 4638 individuals were included in the study, of whom 48% were black.[114] Black patients had significantly lower vitamin D levels than did white patients.[114] Of the 333 patients with Covid-19 positive tests, over two-thirds were black.[114] Multivariate analysis found that a negative Covid-19 test was associated with vitamin D level >30ng/ml (IRR 0.97 (95% CL=0.94-0.99; P=0.008) per 1-ng/ml increase in vitamin D) with an even greater effect in black patients.[114] The authors found that 40ng/ml, rather than 30ng/ml, was the level at which vitamin D became significantly protective against Covid-19, leading them to recommend supplementation with 10,000IU of vitamin D_3/day.[114]

Using a 987,849 patient database in Florida, Katz, Yue, and Xue searched ICD 10 codes for Covid-19 patients for vitamin D deficiency, diabetes, obesity, malabsorption, and dental diseases diagnosed in the previous 5 years.[115] The researchers found that 887 had a Covid-19 diagnosis, 31950 had vitamin D deficiency, and 87 had both.[115] Those with both were more likely to be male, and only 12% were white.[115] Vitamin D deficient patients were 4.6 times more likely to test Covid-19 positive than patients without this diagnosis.[115] The association remained highly significant ($p<0.001$) even after controlling for all comorbidities.[115] After adjusting for age, it was determined that patients diagnosed as vitamin D deficient were 5 times more likely to

be infected with SARS-CoV-2 as those without this diagnosis (OR=5.155) 95% CI 3.974-6.688, P<0.001).[115]

C. Evidence based on meta-analyses and systematic reviews

At least 26 systematic and basic review and meta-analysis papers on the topic of the relationship between Covid-19 outcomes and vitamin D levels have been published to date (see Table 1, pages 18-19).

An early meta-analysis of 10 case control studies found, in the pooled analysis, that vitamin D deficiency or insufficiency, defined as 25(OH)D < 30ng/ml, significantly increased the odds of contracting Covid-19 (OR=1.43,95%, CI=1.00–2.05).[116] In addition, the average vitamin D level of Covid-19 positive groups was significantly lower than that of negative groups (SMD=-0.37,95% CI=-0.52 to -0.21, I^2=89.6%).[116]

Oscanoa's group evaluated the 23 observational studies published by the end of 2020 to determine the relationship between Covid-19 severity and mortality and vitamin D levels.[4] Pooled results demonstrated that vitamin D deficiency is associated with significantly increased risks of poor Covid-19 outcomes, with 17 studies addressing severe Covid-19 (RR 2.00; 95% CL=1.47–2.71) and 13 addressing mortality (RR 2.45; 95% CL=1.24–4.84).[4]

The first meta-analysis to include only intervention studies which all had a very low risk of bias found that vitamin D supplementation clearly decreases Covid-19 mortality (pooled OR=0.264, 95% CI=0.099–0.708, p=0.008) and two studies demonstrated a significant (p=0.001) decrease in OSCI severity scores.[117] The four studies included in this analysis will be further discussed in the next section.

A large rigorous meta-analysis of studies examined 39 cohort, randomized controlled trials, and cross-sectional studies as of 26 Nov 2020, excluding all preprints.[31] ORs and CIs were reported for each outcome by pooling studies based upon the statistical adjustments used by the authors.[31] Kazemi, et al., found that vitamin D was strongly associated with Covid-19 mortality and severity, and is also likely a factor in infection rates, although those study designs were less strong.[31] The evidence for decreasing inflammatory markers and hospital, ICU, and ventilator utilization was less clear.[31] In one study, the probability of a fatal outcome was ten times higher if 25(OH)D was less than 10ng/ml than if it was more than 10ng/ml.[31,118]

Authors of a June 2021 meta-analysis of 13 vitamin D intervention studies that reported ICU admissions, severity and/or fatality rates for Covid-19 patients found that cholecalciferol (11 studies) or calcifediol (2 studies) supplementation significantly reduced risk of ICU admissions/mortality (pooled OR 0.41, 95% CL=0.20, 0.81, p=0.01, I2=66%, random-effects model) and adverse outcomes (pooled OR 0.27, 95% CL= 0.08, 0.91, p=0.03, 2I=80%, random-effects model).[32]

A meta-analysis in July 2021 found 13 RCTs, quasi-RCTs and observational studies meeting the authors' quality criteria which included individual vitamin D levels upon testing for infection. The researchers determined that low 25(OH)D is statistically significantly associated with risk of Covid-19 infection, recommending supplementation for high risk and deficient groups.[119] Another meta-analysis published in June evaluated 23 studies both qualitatively and quantitatively, finding that Covid-19 patients all had low mean 25(OH)D levels, and D deficiency was associated with a 3x higher risk of infection and 5x higher risk of severe Covid-19.[120]

The clear consensus of these meta-analysis authors is that there is a strong relationship between vitamin D levels and Covid-19 outcomes. The studies reviewed demonstrated that

vitamin D supplementation and/or higher vitamin D levels are associated with decreased chances of developing Covid-19 infection; decreased chance of developing severe Covid-19; decreased chance of requiring oxygen, hospitalization, ICU care, or mechanical ventilation; and decreased chance of death due to Covid-19 (see Table 1, pages 18-19). Vitamin D supplementation is also associated with a decrease in fibrinogen, an inflammatory marker.[78]

Despite this powerful evidence, public health officials continued to call for randomized controlled trials. The question of causation had to be addressed, particularly for those unfamiliar with the biological plausibility of the relationship.

IV. Evidence that vitamin D is a causal factor in poor Covid-19 outcomes

Calls for randomized controlled trials to prove a causal relationship cannot, however, be heeded by most vitamin D experts. Vitamin D is not a novel drug which may or may not be beneficial, but rather, it is known to be essential to human health. A scientist who believes that low vitamin D levels are responsible for high mortality rates cannot ethically withhold this life-saving substance from the placebo group.[121,122]

A. Early causal modeling studies

This ethical dilemma was solved in 1965 by Sir Bradford Hill, who developed a causal model to demonstrate that smoking is a cause of lung cancer. Hill's criteria were used to demonstrate that low vitamin D is a cause of severe Covid-19 in a MEDLINE indexed article in May of 2020.[123] Vitamin D met all but one of Hill's criteria, specificity, which it failed only because vitamin D deficiency is ubiquitous.[123] Later authors concurred that the evidence to date satisfied Hill's criteria (strength of association, consistency, temporality, biological gradient, plausibility, and coherence), clearly demonstrating causality.[83]

The idea that robust vitamin D levels are merely a marker for good health (a "bystander") has persisted in part because sick people are less likely to spend time outdoors, and because vitamin D is consumed in slightly higher quantities during illness. Davies, Garami, & Byers noticed a strong relationship between early Covid-19 fatalities and latitude.[124] This observation led them to create a causal inference framework specific to testing the vitamin D hypothesis.[124] The model produced strong evidence that Vitamin D was a cause of Covid-19 fatalities, and moderate evidence for vitamin D causing cases, with causation fitting the data for 16 predictions.[124] The bystander model for vitamin D was strongly contradicted by the data for 14 predictions.[124]

B. Intervention studies

Calls for RCTs continued, and several have been conducted. However, the study designs often reveal a lack of insight into how vitamin D is utilized by the body. Giving oral cholecalciferol to patients who already have severe Covid-19 is clearly unlikely to be effective (see section IIA, pages 3-4, Defining vitamin D). In addition, the response curve for vitamin D is S-shaped, not linear.[121,125] Therefore, providing vitamin D to individuals whose levels are already replete will not demonstrate a benefit, and giving inadequate doses to people who are severely deficient may not bring their levels up high enough to provide immune benefits.[121,125] Because either of these common scenarios can make an intervention that could be life-saving for people whose vitamin D levels are in between these extremes appear ineffective, and because

individual supplementation response is influenced by genetics, obesity, diabetes, etc., trials must be guided by participant 25(OH)D levels.[16,125,126]

Vitamin D requirements for immune health are far higher than those for bone health.[16,58] Virtually any medication can be "proven" ineffective by a study in which only 1/10 the required dose is given. Dosing intervals are also of critical importance in vitamin D trials; studies have shown that large infrequent boluses can prevent the formation of new calcifediol for at least 28 days, and are instead broken down by the body relatively quickly, with the by product, calcitroic acid, being indistinguishable from active calcifediol to most 25(OH)D tests.[36,37,41,74,122,127] Finally, in recent Covid-19 trials, some large-seeming studies had relatively few participants who were actually exposed to SARS-CoV-2 during the study period.[128]

Beginning in late 2020, an increasing number of innovative intervention studies were published demonstrating a clear causal relationship between low vitamin D levels and worse Covid-19 outcomes. (See Table 2, pages 20-21, for summaries of these studies as of June 2021, along with odds ratios, hazard ratios, confidence intervals, and other statistical findings.)

Several researchers evaluated Covid-19 outcomes for individuals who were already supplementing with vitamin D. Annweiler published two quasi-experimental studies which found that if frail elderly people in long term care or in a hospital geriatric ward had been given a cholecalciferol bolus (50,000-80,000IU) more recently, their subsequent cases of Covid-19 were statistically significantly less likely to be as severe when compared with their counterparts who had not had the supplemental D_3 as recently.[79,129] Both studies also found that the recently supplemented frail elderly patients were over three times less likely to die than those who did not receive supplements recently.[79,129] Cangiano's team found that, when compared with no vitamin D supplements, routine vitamin D_3 supplements of any kind also decreased the risk of Covid-19 mortality in nursing home residents to less than a third that of the unsupplemented group.[130]

In a study in which only 19 hospitalized patients had a history of any vitamin D supplementation (usually monthly) and 82% of the patients had very low 25(OH)D levels on admission (mean 13.8ng/ml), Hernandez, et al., found that vitamin D seemed to improve several indicators of Covid-19 severity, but none reached statistical significance.[131]

Oristrell compared the electronic health records (EHR) of 6252 patients who were on calcitriol for severe kidney disease or hypoparathyroidism with matched controls, finding a significant ($p=0.002$) and progressive decline in risk of severe Covid-19 with increasing doses of calcitriol.[132] End stage renal disease patients were also significantly less likely to have become infected with Covid-19 ($p=0.010$).[132] The likelihood of fatal Covid-19 was decreased ($p=0.031$) for all patients taking calcitriol.[132]

During the height of the Covid-19 pandemic, Fasano's group conducted telephone interviews of 1486 Parkinson's patients who had attended their practice, finding that the 329 who regularly took cholecalciferol supplements were about half as likely to have tested positive for Covid-19.[133]

Two groups of researchers mined large EHR databases to explore the relationship between vitamin D supplement prescriptions and testing positive for Covid-19.[134,135] Ma, et al., looked at 8207 records from over 10 years prior to the pandemic, while Israel looked at 2794 records from within 4 months of testing.[134,135] Ma, et al., found that "habitual" vitamin D supplementation was associated with a 34% decrease in Covid-19 cases, while Israel et al., found that recent supplementation with vitamin D_3 drops decreased Covid-19 cases, but not with tablets, perhaps because the tablets were so costly that they were likely to be prescribed only to patients with severe vitamin D deficiency.[134,135]

Loucera, et al., mined a database with 16401 hospitalized Covid-19 patients to see if the 1203 who were prescribed vitamin D supplements in the 15 or 30 days prior to their hospitalization were more likely to survive than those who were not prescribed D.[136] They found a significant reduction in mortality, which was larger if the form of vitamin D was calcifediol or the prescription was only 15 days prior to hospitalization p=0.003).[136]

Two research groups in India each gave 60,000IU/day of cholecalciferol to outpatients who tested positive for Covid-19 and compared their inflammatory marker levels with controls.[77,78] Lakkireddy, et al., found that vitamin D_3 decreased CRP, LDH, IL-6, Ferritin, and the N/L ratio with a significance of p=0.0004 or better, while in the control group several of these markers increased and only CRP levels improved.[77] Rastogi, et al., found that in the D_3 supplemented group fibrinogen decreased more quickly (p=0.007) and that three times as many in the treatment group achieved Covid-19 PCR test negativity by day 21 (62.5% vs 20.8%, p=0.018).[78] The more rapid viral clearance was expected to result in less chance of spreading Covid-19 and a more rapid return to work.[78]

Patients were given a one-time large dose of cholecalciferol after hospitalization for Covid-19 in three studies.[137–139] In two of these intervention studies plus a third in which lesser doses of cholecalciferol were given at regular intervals, patients with 25(OH)D levels less than 20ng/ml were more likely to receive supplementation.[138–140] It is quite possible that many of these patients subsequently enjoyed higher 25(OH)D levels than some of the initially "vitamin D sufficient" patients.[138–140] In a fourth study, the one-time large dose of cholecalciferol was given an average of 10.3 days after symptom onset.[137] It is likely that much of the cholecalciferol given to seriously ill patients in these four studies was immediately broken down into calcitroic acid and that calcifediol levels were actually depressed as a result of the boluses.[36,37,41] Despite this concern, none of the treatment groups fared worse than the controls.[137–140] The researchers who gave lesser doses of cholecalciferol at regular intervals found that this treatment led to significantly (p=0.001) fewer mortalities when compared with unsupplemented patients.[139]

Two research groups compared D_3 supplementation at 1000IU/day with a higher daily dose in hospitalized Covid-19 patients to evaluate the differences in severity of symptoms.[141,142] In a case series with four patients, Ohaebulam, et al., found that 50,000IU/day led to shorter lengths of stay, lower oxygen requirements, decreased CRP and LDH, and a dramatic drop in IL-6 compared with patients who received 1000IU/day, whose 25(OH)D levels did not increase.[141] The second study was a 69 patient randomized controlled trial in which, again, 25(OH)D levels did not increase for the 1000IU/day group.[142] These researchers found that 5000IU/day for two weeks led to significantly quicker resolution of cough (p=0.039) and loss of taste (p=0.035).[142]

A historical cohort study compared previously treated hospital patients with the next 17 patients, who were managed with the same treatment protocols, but with the addition of 1000IU D_3 + 500mcg B_{12} + 150mg magnesium (DBM) daily, assessing for new need for oxygen or ICU care.[143] New oxygen need decreased from 61.5% to 17.6% (multivariate-adjusted p=0.006), and the need for ICU care decreased from 30.8% to 5.9%.[143] The authors called for a randomized controlled trial of their DBM treatment protocol.[143]

In an anecdotal published report, physicians at the Iranian Hospital in Dubai, UAE described their Covid-19 vitamin D supplementation protocol, which is individualized according to the patient's weight and 25(OH)D level.[59] Asserting that typical endocrine societies guidelines suggest that 40-60ng/ml is the ideal 25(OH)D level, they routinely aggressively supplement with 70-100IU of D_3 per kg per day in their neuro-ophthalmology department without any cases of toxicity.[59] Finding that, despite their high risk, none of their patients who contracted Covid-19

had a severe case, they recommended this dosage plus an initial bolus of 300,000IU IM for all Covid-19 admissions, which they report resulted in the ICU being completely cleared of Covid-19 patients.[59]

Researchers for three studies conducted in several hospitals in Spain addressed the problem of slow metabolism of cholecalciferol by giving patients moderately high doses of calcifediol early in their hospitalization and at regular intervals.[144–147] This protocol consistently resulted in a dramatic decline in ICU admissions and mortality rates. In the pilot study, the ICU admission rate for the treated patients was 2% with no fatalities, compared with a 50% ICU admission and 7.7% fatality rate for the untreated patients.[144] A second trial of the same calcifediol protocol resulted in a decrease in fatalities from 20% for the control group to only 5% in the treatment group.[145] The third study resulted in 4.5% of the vitamin D supplementation group being admitted to ICU, compared with 21% in the control group.[146] In 53 cases, physicians believed that an ICU patient in the control group might be rescued by giving them calcifediol.[146] Mortality for the original study groups was 4.7% for the treatment group and 15.9% for the control group.[146] If the 53 control group patients who received calcifediol only after being admitted to the ICU are added to the treatment group, the mortality for the treatment group increases to 7.2% and mortality for the control group decreases to 13.9% (p=0.001).[146] The researchers noted that the patients who died had lower baseline 25(OH)D levels (9ng/ml) than the ones who survived (13ng/ml).[146]

These intervention studies all strongly support the hypothesis that low serum calcifediol levels are a significant causal factor in poor Covid-19 outcomes.

C. Future Research Opportunities

Several of the research studies described above show enough promise that expanding upon them is likely to be beneficial. In addition, much more needs to be learned about the relationship between supplementation and calcifediol levels.
Research priorities during the Covid-19 pandemic are:

- A rigorous, multi-center study of the calcifediol supplementation protocol used in the three highly successful Spanish studies for hospitalized Covid-19 patients
- A longitudinal study comparing individuals who take daily D_3 supplements at various doses to determine the optimal usual dose based upon percent body fat
- A large EHR study of individuals with 25(OH)D levels taken within the past year, comparing Covid-19 infection, hospitalization, ICU admission, and fatality rates between those with levels over 50ng/ml and those the levels that are 20-30ng/ml.

V. Specific recommendations for Vitamin D supplementation to improve Covid-19 outcomes

Several groups of experts have called for widespread vitamin D supplementation to help prevent poor Covid-19 outcomes. The largest group is VitaminDforAll.org, a coalition representing 220 professors, medical doctors, and PhD vitamin D experts from 33 countries.[106] Every signatory recommends universal supplementation with 4000IU/day of vitamin D_3 (or at least 2000IU/day) in the absence of testing, with the goal of raising 25(OH)D levels to at least 30ng/ml.[106] Those at especially high risk for deficiency (due to weight, frailty, dark skin) are encouraged to consider doubling that dose.[106] Individuals who have not previously taken vitamin D supplements should take D_3 10,000IU/day for 2-3 weeks initially, or until serum 25(OH)D

levels can be drawn, then drop to the above amounts.[106]

The Italian Academy of Medicine of Turin letter, signed by a group of 152 Italian professors and physicians, also calls for universal supplementation with D_3 4000IU/day, but with a goal of acquiring 25(OH)D levels of 40ng/ml.[148] The French La Revue du Praticien, signed by 73 French authors with the support of 6 national scientific societies, calls for prophylaxis with D_3 of 1200IU/day, or double that amount for obesity, noting that 4000IU/day is safe.[149] The Health Committee of the Legislature of Ireland (Oireachtas) recommends daily vitamin D supplementation of 800-1000IU for the entire adult population, with higher doses for vulnerable groups, along with public education and encouragement, including reducing the cost and making supplementation an opt-out.[150,151]

The vitaminDforAll.org coalition and Italian Academy of Medicine of Turin letter both recommend that all hospitalized Covid-19 patients have 25(OH)D levels drawn upon admission and be treated with calcifediol or D_3, using a protocol for calcifediol such as the one the three Spanish trials used so successfully or the cholecalciferol 60,000IU/day used successfully by Rastogi, et al.[106,148] The French La Revue du Praticien recommends D_3 100,000IU upon diagnosis, to be repeated 7 days later.[149]

Based upon the totality of the evidence, the vitaminDforAll.org recommendation:

- **4000IU per day as maintenance for all adults without medical contraindications**
- **10,000IU/day for 2-3 weeks initially for those not previously supplemented**
- **adjusted to meet a goal serum 25(OH)D of at minimum 30ng/ml**

should be safe (all studies support this), and is the most likely to be effective.

CONFLICT OF INTEREST DISCLOSURE

Linda Benskin is the sole author of this chapter, with no conflicts of interest to declare.

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ABBREVIATIONS

ARDS – acute respiratory distress syndrome
RAS – renin-angiotension system
EHR – electronic health record

Table 1 - Summary of Systematic and Basic Reviews and Meta-analyses Specific to Covid-19 and Vitamin D				
Reference	Search end date	Number and types of evidence	Specific studies included (first author)	D related conclusions
Akbar *et al*, 2021[152]	9Dec20	14 observational cutoff of 20-30ng/ml	Abrishami, Backtash, Cereda, Hastie, Hernandez, Im, Jain, Katz, Luo, Maghbooli, Meltzer, Merzon, Radujkovic, De Smet	Low D sig assoc with infection, severity, & fatality
Artusi *et al*, 2021[153]	10Jan21	16 Parkinson's observational studies	Only one study in this meta-analysis included vitamin D: (Fasano, Lombardy, Italy)	22.9% vs 12.4% case rate with D supplementation
Bassatne *et al*, 2021[154]	20Jan21	31 observational D 3 intervention trials	Removed Maghbooli dt expression of concern Removed studies that used higher cutoffs for low D than authors required, etc.	No significant findings. Maybe calcifediol in ICU.
Benskin 2020[16]	16Jun20	47 human research studies of any type	Basic review – summaries of each study See list – early studies – none interventional	D assoc with high mortality:16 studies, cases: 17, higher severity: 10
Chamberg o-Michilot *et al*, 2021[155]	1Apr21	4 case controlled 2 cross-sectional	Fasano & Sainz-Amo included D in reports Both found that D supplementation lowers risk for Covid-19 cases, not stat sig in Sainz-Amo	Low D significantly increases risk of Covid-19 infection
Chen *et al*, 2020[156]	1Oct20	6 with multivariate analysis	Chang, Hastie, Meltzer, Mendy, Merzon, Radujkovic,	Low D assoc. with incr. infection: 47%, hospital: 83%, poss. death, no dose response
Damayanthi *et al*, 2021[157]	2020	3 related to D specif.	Tan, Annweiler, Annweiler	Each study result
Das *et al*, 2020[158]	3Nov20	11 studies, cohort, cross-sectional, case-control, no RCTs.	Abishami, Maghbooli, Radujkovic, Hastie, Otros, Merzon, Meltzer, Ye, Kaufman, D'Avolio, Baktash (authors are doing major revision)	5.84x >chance die 2.2x >chance severe, also > chance infection
Drame *et al*, 2021[159]	15Mar21	11 age 60+ only 4 supplement or no 7 deficient or no	Annweiler, Annweiler, Giannini, Tan (age 60+ data extracted), Baktash, Carpagnano, Cereda, Hars, Macaya, Radujkovic, Sulli	Overall, studies support D for O_2 & vent needs, severity, & death
Ghasemian *et al*, 2021[120]	18Dec20	23 for quantitative and qualitative analysis	Meltzer, Merzon, Nicola, Faul, Carpagnano, Macaya, Hamza, Karahan, Abdollahi, Arvinte, Cereda, Panagiotou, Radujkovic, Hernandez, Jain, Im, Baktash, Vassiliou, Ye, Maghbooli, Ling, Luo, Karonova,	Covid-19 patients all had low mean 25(OH)D levels. D deficiency was associated with a 3x higher risk of infection and 5x higher risk of severe Covid-19.
Grove *et al*, 2021[160]	10Jun20	SARS, MERS, Covid-19 yielded only 4 quant, 12 qualitative	Quant: only D'Avolio, Hastie, Ilie, Fasano: search should have found more. Qual: not listed because they had not yet passed the peer-review process at time of publication	It is speculative to even consider that vitamin D could have a role.
Kazemi *et al*, 2021[31]	26Nov20	39 cohort, RCT, case-control or cross-sectional -no preprint Very rigorous review	Bahat, Baktash, Blanch-Rubio, D'Avolio, De Smet, Ferrari, Hernandez, Im, Kerget, Jain, Mardani, Meltzer, Merzon, Sun, Ye, Yilmaz, Abrishami, Anjum, Annweiler, Luo, Annweiler, Arvinte, Bagheri, Castillo, Cereda, Haraj, Faul, Goncalves, Hamza, Karahan, Saronova, Macaya, Maghbooli, Panagiotou, Pizzini, Perez, Radujkovic, Rastogi, Carpagnano	D assoc with severity: definitely mortality: yes infection: yes ICU admit, vent, hosp, & inflam: results inconsistent
Liu *et al*, 2021[116]	25Sep20	10 observational (case control) studies	Baktash, Avolio, Hastie, Raisi-Estabragh, Chodick, Im, Mardani, Merzon, Ye, Meltzer (Hastie eliminated due to age of data)	Low D assoc with increased risk lower D → PCR+
Mercola *et al*, 2020[83]	15Oct20	14 observational 3 large population	Hastie, D'Avolio, Panagiotou, Carpagnano, Im, Karonova, Tort, Baktash, Hastie, Radujkovic, Pizzini, Macaya, Ye, Large population: Merzon, Meltzer, Kaufman	Evidence is strong for D assoc with incidence and severity
Munshi *et al*, 2020[161]	8Jun20	6 including MedRxiv and case series	Lau, D'Avolio, Tian, Faul, De Smet, Prinzon all from April and May 2020	Pooled results show D influences prognosis (signif)
Nikniaz *et al*, 2021[117]	16Dec20	D supplementation 4 RCT & quasi	Annweiler, Annweiler, Castillo, Rastogi – all very low risk of bias according to JBI	2: lower mortality Improved severity 1: ICU, fibrinogen

Oscanoa *et al*, 2021[4]	Dec20	23 studies all observational	Carpagnano, Panagiotou, Alipio, De Smet, Lau, Radujkovic, Baktash, Mardani, Pepkowitz, Macaya, Hars, Ye, Yilmaz, Im, Hernandez, Campi, Abrishami, Walk, Karonova, Luo, Cereda, Jain, Karahan	Deficiency assoc with higher risks of severe & mortality
Pal *et al*, 2021[32]	8 Jun21	13: ICU & death only 3RCTs;10observation	Annweiler, Annweiler, Ling, Giannini, Hernandez, Jevalikar, Cereda, Alcala-Diaz, Lohia, Cangiano, Castillo, Murai, Lakkireddy	D supplem assoc with reduced ICU, severity, mortality
Pereira *et al*, 2021[162]	9Oct20	27 observational	Alipio, Baktash, Carpagnano, Cunat, D'Avolio, Darling, Lau, Faniyi, Faul, Hastie, Karonova, Macaya, Maghbooli, Mardani, Meltzer, Smet, Mendy, Merzon, Panagiotou, Pinzon, Pizzini, Radujkovic, Raharusun, Raisi, Sun, Im, Glicio	D deficiency assoc w severe, hosp, & mortality, but not infection dt Hastie & Darling
Petrelli *et al*, 2020[163]	31Jan21	35 Observational only 8 supplement effect	Abdollahi, Abrishami, Alguwaihes, Annweiler, Annweiler, Baktash, Barassi, Bennouar, Blanch-Rubio, Cangiano, Carpagnano, Cereda, Chang, De Smet, Demir, Castillo, Ferrari, Giannini, Hastie, Hernandez, Jain, Karahan, Katz, Kaufman, Li, Ling, Lohia, Luo, Ma, Macaya, Maghbooli, Mardani, Meltzer, Mendy, Merzon, Pal, Panagiotou, Radujkovic, Raisi-Estabragh, Szeto, Tan, Vessiliou, Ye	D deficiency associated with infection, severity, & fatality rates
Rothenberg *et al*, 2021[164]	13 Jan 21	All types, only elderly	Benskin, Castillo, Kaufman, Radujkovic, Pizzini – all of which were discounted by the authors. Omitted at least 3 intervention studies on elderly, D and Covid-19 found using their exact search terms & dates (Annweiler, Annweiler, and Tan)	Narrative review – inconclusive
Szarpak *et al*, 2021[119]	10May21	RCTs, quasi-RCTs, and observational with 25(OH)D levels	Abdollahi, Aguwalhes, Al-Daghri, Baktash, D'Avolio, Hernandez, Im, Livingston, Mardani, Merzon, Raisi-Estabragh, Sulli, Ye	Low 25(OH)D is statistically significantly associated with risk of Covid-19 infection. Supplements of vitamin D are indicated, especially for high-risk and deficient groups.
Shah *et al*, 2021[165]	17Dec20	3 RCTs only	Murai, Hernandez, Castillo	Insufficient studies
Stroehlein *et al*, 2021[166]	1Mar21	3 RCTs only	Murai, Hernandez, Castillo	May decrease ventilator need
Teshome *et al*, 2021[167]	20Dec 20	14 qual, of these, 8 quant*	Meltzer,* Raharusun, Merzon,* Hastie, De Smet,* D'Avolio, Abdollahi,* Ye,* Hernandez,* Kaufman,* Yilmaz,* Maghbooli, Panagiotou, Alguwaihes,	D deficiency was signif assoc with infection risk (80% more likely)
Wang *et al*, 2021[168]	3Dec20	17 observational	De Smet, Carpagnano, Jain, Hars, Cereda, Luo, Hernandez, Abrishami, Ye, Baktash, Mendy, Im, Mardani, Macaya, Pizzini, , Radujkovic, Anjum	D deficiency signif assoc with hosp, mortality, stays, not ICU admission
Yadav *et al*, 2021[169]	5Jun20	3 chart reviews	Ilie, Hastie, D'Avolio	Only circumstantial evidence
Yisak *et al*, 2021[170]	Sept20	9 observational (each study is described)	Mendy, Hastie, Raisi-Estabragh, Ali, Merzon, Daneshkhah, Carpagnano, Entrenas Castillo, Fasano	7 with recent D: assoc infection, severity, & death

Table 2 – Summary of Intervention Studies						
Study Setting	Study Type: Intervention	N/ total	Outcomes Measured	Results	Recommendation	
Hospital	Retrospective cohort: Calcifediol 0.266mg x2 at admit + day 3,7,14,21,28	79/ 537	Mortality	5% vs 20% OR=0.22, 95% CI=0.08 - 0.61, p<0.01 MVA: OR=0.16, 95% CI=0.03 - 0.80 sig	Conducting large RCT of this calcifediol treatment	Alcala-Diaz *et al*, 2021[145]
Nursing home	Quasi-experimental: 80,000IU D_3 <-1-4wks prior to Covid vs >4wks	57/ 66	Mortality OSCI score	Mortality: 17.5% vs 55.6% p=0.023 HR_{adj} =0.11, 95% CI:0.03 - 0.48, p=0.003 Recent D: 7.8% vs 33.7% p=0.023 OSCI: β=-3.84 95%CI= -6.07- -1.62, p=0.001	RCTs underway (population is extremely frail elderly)	Annweiler *et al*, 2020a[79]
Hospital geriatrics	Quasi-experimental: 1: D_3 50,000IU/mo or 80,000IU-100,000IU/2-3 mo; 2: 80,000IU D_3 stat; 3: no supplements	29/ 16/ 32/ 77 tot	Mortality OSCI score	No sig. differences between groups 2 and 3 Mortality: 6.9% vs 18.8% vs 31.3% p=0.02 Group 1 (vs 3) HR = 0.07, p = 0.017 OSCI group 1 vs 3: ≥5 OR=0.08, p = 0.03	Regular supplementation monthly with moderate dose boluses, but not a last-minute bolus, is beneficial. Should test higher one-time dose.	Annweiler et al, 2020b[129]
Nursing home	Observational: Routine D_3 supplements vs no supplements	20/ 98	Mortality	3/20 died in vitamin D group, vs 39/78 without Mortality rate was 15% vs 50% 3/42 deceased vs 17/56 survived: p=0.005	Need RCTs, but with common deficiency, administration of D_3 to elderly seems prudent	Cangiano *et al*, 2020[130]
Hospital	RCT: Calcifediol 0.266mg x2 at admit + day 3,7,14,21,28	50/ 76	Mortality ICU admission	Mortality: 0% vs 7.69% deceased ICU: 2% vs 50% p<0.001 MVRE OR=0.03 95 %CI 0.003-0.25	Expanded study COVIDIOL will include earlier Covid-19 stages and more patients	Entrenas Castillo *et al*, 2020[144]
Community Parkinson's	Observational: of patients regularly taking D_3, how many became infected?	329/ 1486	Covid-19 infection	5.7% vs 7.9% (Cases: vit D vs no vit D) 12.4% vs 22.9% (Vit D: cases vs unaffected) OR_{adj}: 0.56, 95% CI=0.32–0.99] p=0.048	Vitamin D is possibly protective, recommend RCTs	Fasano *et al*, 2020[133]
Hospital	Physicians chose yes/no: D_3 200,000IU/day x 2. More likely if patient had 25(OH)D<20ng/ml, was a smoker, had high D-dimer, had comorbidities	39/ 91	Mortality ICU admission	Never listed outcomes for D treated patients. If comorbidities are seen as confounders: OR_{adj} 0.45 95% CI(0.20–1.22), p = 0.13 If comorbities are seen as effect modifiers: 3+: OR_{adj} 0.18, 95%CI0.04–0.83), p=0.039 (see article for fewer comorbidities)	Authors hypothesize: Two consecutive daily doses of 200,000IU cholecalciferol can significantly improve the outcome in Covid-10 patients with 3 or more comorbidities.	Giannini *et al*, 2021[140]
Hospital	Retrospective case-control: 19 patients took monthly D_3 or calcifediol	19/ 216	Many dependent variables	Supplement group: lower PaO2/FIO2 ratio<300 prevalence, serum ferritin levels, severity index, ICU, length of stay. None sig.	All had low D. Supplemented 21.1ng/ml, unsupplemented 13.8ng/ml. Call for D RCTs.	Hernandez *et al*, 2021[131]
Population	Population study (EHR): obtained D supplements in past 4 months	2794	Covid-19 positive test	D drops decreased risk, tablets sl increased it. Drops: OR=0.905 (95% CI 0.848-0.967) Tablets: OR=1.248 (95% CI 1.152-1.352)	D supplements are also OCT. Tablets are costly, may be a surrogate for D deficiency	Israel *et al*, 2020[134]
Hospital	Prospective nonrandom: Physicians gave one time ~60,000IU D_3 to some with 25(OH)D<20ng/ml	128/ 197	Inflammatory markers, ICU,fatality, severity	Deficient patients: 25(OH)D mean of 9.8ng/ml Dramatically lower levels of inflammatory markers, fatality of 0.8% vs 4.3% None statistically significant.	Did not see any benefit with vitamin D	Jevalikar *et al*, 2021[138]
Outpatient	RCT: vitamin D deficient Covid-19 patients given	44/ 87	Inflammatory markers,	Decreases in CRP, LDH, IL6, Ferritin, and N/L ratio all p=0.0004 or better for D group,	Ongoing study. Raised 25(OH)D to 80-	Lakkireddy *et al*,

	60,000IU D_3/day x 8 days		duration	increased or same for controls except CRP	100ng/ml with benefits and no side effects.	2021[77]
Hospital	Retrospective (EHR): had D_3 "booster" therapy if known 25(OH)D<20ng/ml	151/ 986	Mortality	Booster sig protective (main group's stats): (OR_{adj} 0.25, 95% CI 0.12–0.49), p < 0.001) MV(OR_{adj} 0.13, 95% CI 0.05–0.35, p < 0.001)	Likely most hospitalized with Covid-19 are poor responders to vitamin D, need extra.	Ling *et al*, 2020[139]
Hospital	Retrospective (EHR): Calcifediol or D_3 in preceding 15-30 days	120 3/ 164 01	Mortality	Survival sig more likely if D prior to Covid-19. Survival prob if D up to 30 days prior p=0.032 Survival prob if D up to 15 days prior p=0.003	Calcifediol better than D_3 & 15 days better than 30. Should test long-term too, in RCTs	Loucera *et al*, 2021[136]
Commu nity	Retrospective (EHR): Any D supplementation 10-15 years prior to Covid-19	363/ 820 7	Covid-19 infection	Habitual D suppl. was associated with a 34% decrease in Covid-19 cases (13.5% vs 16.8%) OR_{adj}, 0.66; 95% CI, 0.45–0.97; P = 0.034	Did not find evidence of selection bias. Supplement data was very old. Need new.	Ma *et al*, 2021[135]
Hospital	RCT: Single oral dose of 200,000IU D_3	117/ 237	Hospital length of stay, etc.	No significant differences between groups for any parameter except 25(OH)D levels, up from 21.2 to 44.4ng/ml. ?Calcitroic acid?	No benefit, therefore use of D_3 is not supported. D was given 10.3 days after illness onset.	Murai *et al*, 2020[137]
Hospital	Observational cohort (randomized by ward): Calcifediol 266ug x2 at admit + day 3,7,15,30 *(retracted because it was not randomized by patient)	447 +53/ 838	Mortality ICU admission	Mortality: 4.7% vs 15.9% p=0.0001 OR_{adj} 0.21 [95% CI 0.10; 0.43] add 53 ICU "rescues" OR_{adj} 0.52 [95% CI 0.27;0.99]. ICU: 4.5% vs 21% p=0.0001. OR_{adj} 0.13 [95% CI 0.07;0.23]	ICU admission requirements markedly reduced, mortality decreased by 50%. Vitamin D deficiency is easily modifiable.	Nogues *et al*, 2021[171]
Hospital	4 patient case series: at diagnosis, 1000IU/day or 50,000IU/day for 5 days	4	Lessening severity of ARDS	By day 5 high dose patients had lower O_2 requirements. Had lower lengths of stay. CRP & LDH decreased as 25(OH)D increased. IL6 dropped dramatically. Not so with low dose D.	Looks promising, but the two with 1000IU had diabetes and hypertension (confounders). RCTs should be conducted.	Ohaegbul am *et al*, 2020[141]
Hospital & Commu nity	Retrospective (EHR): Already on calcitriol due to kidney failure or HPTH	625 2/ 12,5 04	Infection Severe Fatal	Inf stage 4&5 only: HR 0.78 95%CI 0.64-0.94, p=0.010 Severe 1.4% vs 1.9%, HR 0.68; 95%CL0.53-0.87, p=0.002 Fatal 1.2% vs 1.7%: HR 0.75; 95%CI= 0.57-0.97; p=0.031	A progressive decline in risk of severe Covid-19 and mortality was seen with increasing calcitriol doses.	Oristrell *et al*, 2021[132]
Commu nity	RCT: D_3 60,000IU/day x 7 days – longer if still low	16/ 40	Viral clearance	62.5% vs 20.18% p<0.018 by day 21. Only other change: Fibrinogen decreased p<0.007	D_3 may help prevent Covid-19 transmission	Rastogi *et al*, 2020[78]
Hospital	RCT: : D_3 1000IU/day or 5000IU/day x 2 weeks	36/ 69	Decreased symptoms	Cough: $_{adj}$6.2 ± 0.8 versus 9.1 ±0.8; p=0.039 Taste: $_{adj}$11.4 ± 1.0 versus 16.9 ±1.7; p=0.035	25(OH)D increased only for 5000IU group. Recommend.	Sabico *et al*, 2021[142]
Hospital	Historical cohort: 150mg Mg + 500mcg B_{12} + 1000IU D_3 daily (DMB)	17/ 43	New need for O_2 or ICU	Needed oxygen: 17.6 vs 61.5%, MV_{adj}P=0.006 OR 0.13 95% CI= 0.03-0.59) Needed ICU: 5.9% vs 30.8% OR 0.20 95% CI= 0.04-0.93	Despite small sample size, DMB seemed to prevent deterioration. Need RCT.	Tan *et al*, 2020[143]

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